

DOCKET NO: ISIS0064-100 (RTS-0175)

PATENT

REMARKS

Claims 1, 2, 4-10, 12-15 are pending in the application. Claim 1 has been amended herein, support for which can be found at, for example, page 5, lines 10-14 of the specification. No new matter has been added. Claims 1, 2, 4-10, 12-15 will remain pending.

Because the amendments to the claims remove issues for appeal (*i.e.*, indefiniteness), Applicants respectfully request that they be entered into the record. See, M.P.E.P. § 714.12.

I. The Claimed Invention Is Not Obvious

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of Ishibashi et al., J. Biol. Chem., 1994, 269, 29897-29902 (hereinafter, the "Ishibashi reference"), Sato et al., J. Biochem., 1998, 123, 1119-1126 (hereinafter, the "Sato reference"), Milner et al., Nature Biotechnol., 1997, 15, 537-541 (hereinafter, the "Milner reference"), and U.S. Patent No. 5,801,154 (hereinafter, the "Baracchini reference"). The Office Action maintains that it would have been obvious to target and inhibit expression *in vitro* by administering oligonucleotides having between 8 and 50 nucleobases targeted to DUSP5. Applicants traverse the rejection and respectfully request reconsideration thereof.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior

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art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would impel one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

Applicants do not question the general motivation to modulate the activity of DUSP5 that may be provided in the Sato and/or Ishibashi references. This general motivation, however, is not what is required to establish a case of *prima facie* obviousness. Rather, the requisite motivation that must be established is a motivating force that "would impel one skilled in the art to do what the patent applicant has done." Indeed, there are many avenues to take when desiring to modulate the activity of a protein involved in a disease pathway. For example, one skilled in the art may choose to investigate the role of peptides/proteins, antibodies, or even small molecules that inactivate DUSP5. Neither the Sato nor Ishibashi references provide any motivation to choose any particular avenue to modulate DSP5 activity, let alone specifically choose oligonucleotide compounds.

What the Office Action appears to suggest is that the claimed invention would have been obvious because it would have been possible to modify DSP5 with oligonucleotide compounds. The mere possibility that the prior art can be modified, however, does not itself provide the requisite motivation to do so. *In re Dien*, 152 U.S.P.Q. 550 (C.C.P.A. 1967) (incentive to seek improvement of existing process held to not render change made by applicant obvious, even where the change was one capable of being made from theoretical point of view). The mere possibility for modification and improvement is not the "motivating force" that the Patent Office Board of Appeals and the Federal Circuit have invariably required. If it were, then no modification would ever lack motivation since some change is always possible. Quite to the contrary, an invention is obvious under the patent laws only when the claimed means for effecting an improvement -- as opposed to the possibility of trying any and all means -- is

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suggested by the prior art. *In re Shaffer*, 108 U.S.P.Q. 326 (C.C.P.A. 1956) (references, viewed by themselves and not in retrospect, must suggest doing what applicant has done). Significantly, neither of the cited references would have motivated persons of ordinary skill to make the substantial modifications that would have been necessary to produce the claimed invention. It is only with the improper use of hindsight and with the benefit of the Applicants' disclosure that one can discern the desirability of the particular invention now claimed.

Again, the alleged motivation, at most, raises an inappropriate "obvious to try" standard. Indeed, the court made it clear that it is improper to reject claims as "obvious to try" where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

In addition to establishing an impelling motivation, to set forth a legally sufficient *prima facie* case of obviousness, the Patent Office must also show that the cited references teach or suggest a claimed invention with a *reasonable expectation of success*. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). The Office Action asserts that one of ordinary skill in the art would have a reasonable expectation of success in finding antisense compounds that successfully inhibit the expression of DSP5 using routine and well established methods, referring to the Milner reference (see, pages 4-5 of the Office Action). The Milner reference, however, does not establish a reasonable expectation of success in obtaining oligonucleotide compounds that would inhibit DSP5 by at least 40%. Indeed, the Milner reference teaches:

Surprisingly, few oligonucleotides gave significant heteroduplex yield. ... These results help to explain the variable success that is commonly experienced in the choice of antisense oligonucleotides. ... We find no obvious features in the mRNA sequence or the predicted secondary structure that can explain the variation in heteroduplex yield.

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(See, Abstract). The Milner reference also teaches:

Taken with our studies these observations make clear the difficulty of finding good candidates for antisense sequences by methods which are not based on experimental measurements.

(See, page 541, first column). Thus, the Milner reference reinforces the notion that there is no reasonable expectation of success of obtaining active oligonucleotide compounds until the experiments are actually carried out. The fact that screening assays are available does not render the claimed invention obvious.

The Office Action appears to conclude that simply because screening assays for evaluating the inhibitory activity of oligomeric compounds are available and may be routine, one skilled in the art would, thus, have a reasonable expectation of success in obtaining oligomeric compounds that would inhibit the expression of dual specific phosphatase 5 by at least 40%. That screening assays are available and routine would only provide a reasonable expectation of success of being able to screen oligomeric compounds for inhibitory activity. The mere fact that screening assays are available and routine, however, has no bearing on whether one skilled in the art would have a reasonable expectation of success in obtaining oligomeric compounds that inhibit the expression of a particular gene by a particular amount. Indeed, it is not possible to currently predict the level of inhibition of expression achieved with any particular oligomeric compound prior to carrying out the appropriate experiments. Applicants submit herewith a Declaration of Dr. Bennett, one of skill in the art of oligonucleotide technology. In paragraph 3, Dr. Bennett declares that it is not possible to currently predict the level of inhibition of expression achieved with any particular oligomeric compound prior to carrying out the appropriate experiments. In paragraph 5, Dr. Bennett declares that it is not reasonable to expect for any particular gene or mRNA that oligomeric compounds having at least 40% inhibition in the expression will be obtained. Thus, simply because screening assays are available and may be routine, one skilled in the art would not have a reasonable expectation of success in obtaining oligomeric compounds that will inhibit the expression of dual specific phosphatase by at least 40%. Therefore, even if one skilled in the art were motivated to combine the cited references in the manner indicated in the Office Action (and Applicants maintain that no such motivation has been established), one skilled in the art would not have had a reasonable expectation of success.

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In view of the foregoing, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness. In particular, the Office Action has failed to provide any motivation that would impel one skilled in the art to modify the cited references so as to produce Applicants' claimed inventions with a reasonable expectation of success. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

II. The Claims Are Clear And Definite

Claims 1, 12, 13, and 15 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action, at page 2, alleges, "In claim 1, lines 1 and 3, the metes and bounds of the term 'compound' cannot be determined." Although Applicants respectfully disagree, claim 1 has been amended herein to recite "oligomeric compound." The metes and bounds of the term "oligomeric compound" are definite. Indeed, the term "oligomeric compound" is a term of art that is quite well recognized by those skilled in the art and can be found in numerous dictionaries.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.


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III. Conclusion

The claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6914 to clarify any unresolved issues raised by this response.

Respectfully submitted,


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